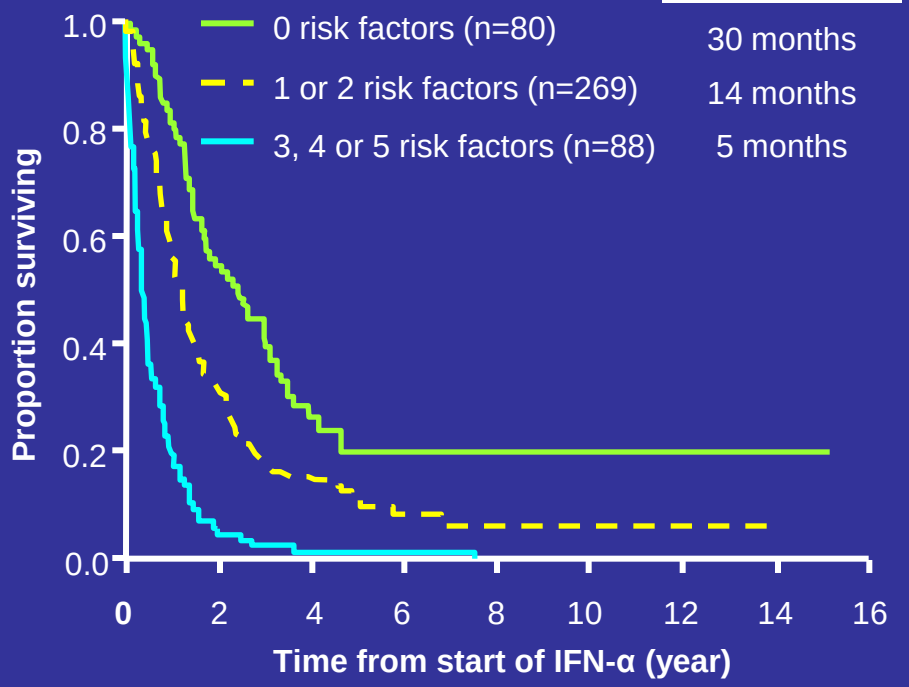
The trial and tribulations of predictive biomarkers in metastatic RCC.

Professor Thomas Powles
Renal cancer lead for London Cancer
Barts Cancer Institute and Royal Free Hospital
UCL and QMUL.

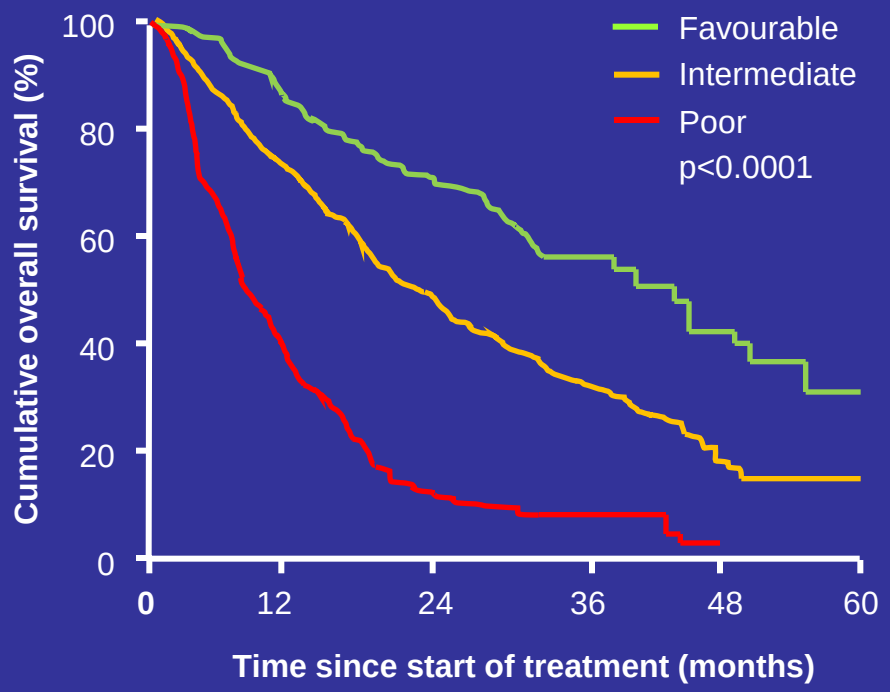



Prognostic models biomarkers in the era of targeted therapy.

MSKCC model[1]



Heng model[2]



Prognostic markers assessed[1,2]

We Still don't have any good predictive markers.

1. Motzer RJ, *et al. J Clin Oncol* 2002;20:289-296.
2. Heng DY, *et al*. *Lancet Oncol* 2013;14:141-148.

Biomarker development

Predicative biomarkers are treatment specific

- In breast cancer HER-2 is associated with a poor outcome i.e. it is prognostic.

- Herceptin is a monoclonal antibody which targets HER-2.

- Patients who over-express HER-2 respond to Herceptin while those who do not. Therefore HER-2 is a predictive biomarker.

Prognostic Implications of BAP1 & PBRM1

Mutation Found	Median OS (years, (CI))
PBRM1	**5.4 (4.0-6.8)**
BAP1	**2.5 (1.3-3.7)**
BAP1 / PBRM1	**0.2 (0.0-1.2)**
Other	**5.8 (4.6-7.0)**

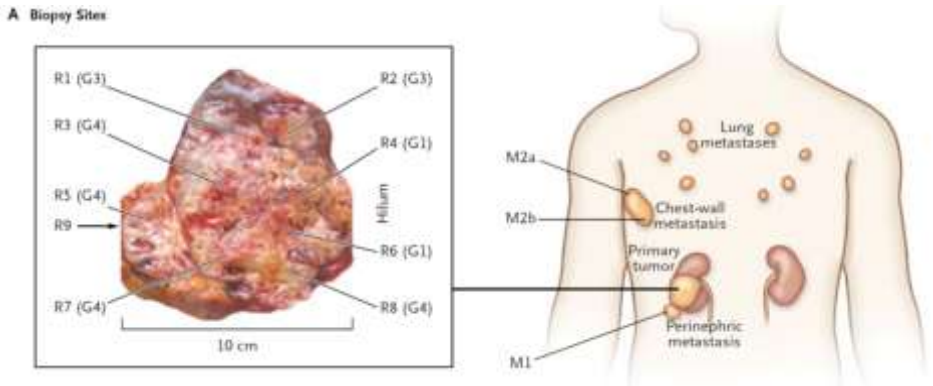
- **Mutations**
- **BAP1 less frequent than PBRM1 mutation**
- **Mutations in BAP1 & PBRM1 rarely found together**
- **Molecular classification of RCC on horizon**
- **Pathway deregulation differs between groups**

Kapur et al., ***Lancet Oncol*** **2013; 14: 159–67**

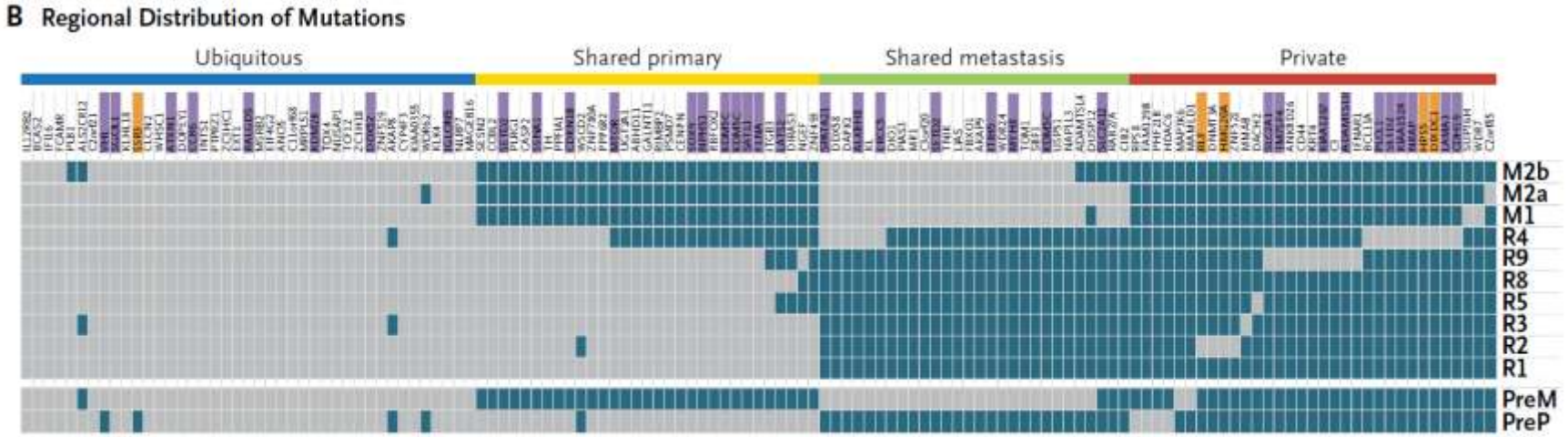
In renal cancer the targets of VEGF and mTOR inhibition are not prognostic.

- The exact mechanism of the drugs its not known.
- The role targets of the drug (tumor, stromal or vascular) remain unknown.
- Protein analysis in this setting has not been helpful for predictive biomakers.

Intra-tumoural heterogeneity: A key challenge in the validation of genetic biomarkers



Sites of core biopsies and regions harvested from nephrectomy and metastasectomy

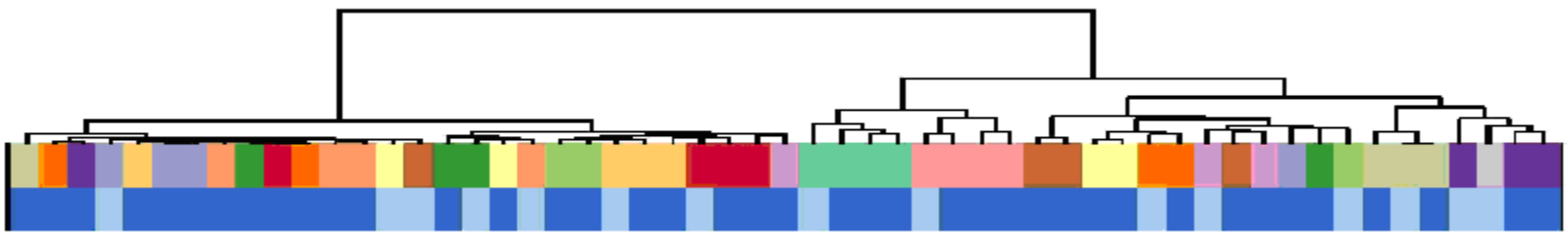


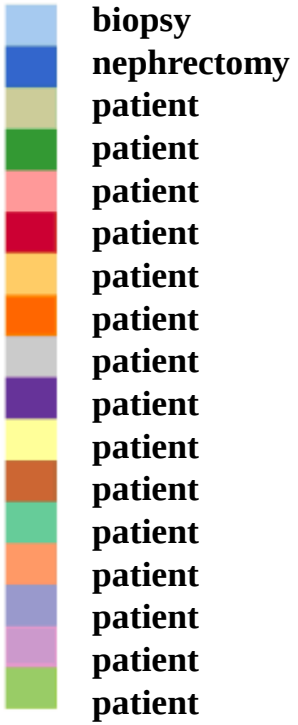
Confidential

1. Gerlinger M, *et al. N Eng J Med* 2012;366:883-892.

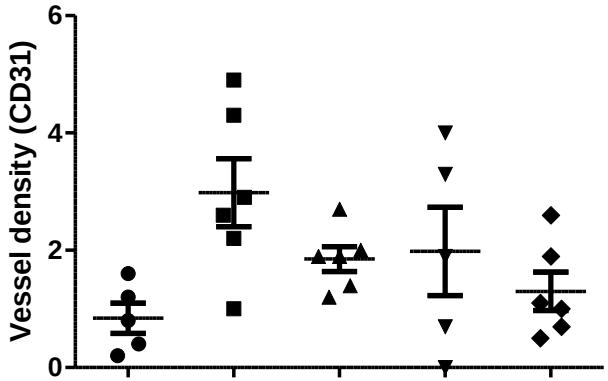
Heterogeneity of biomarker expression in individual patients.

A lack of hieratical clustering with CGH array from multiple biopsies

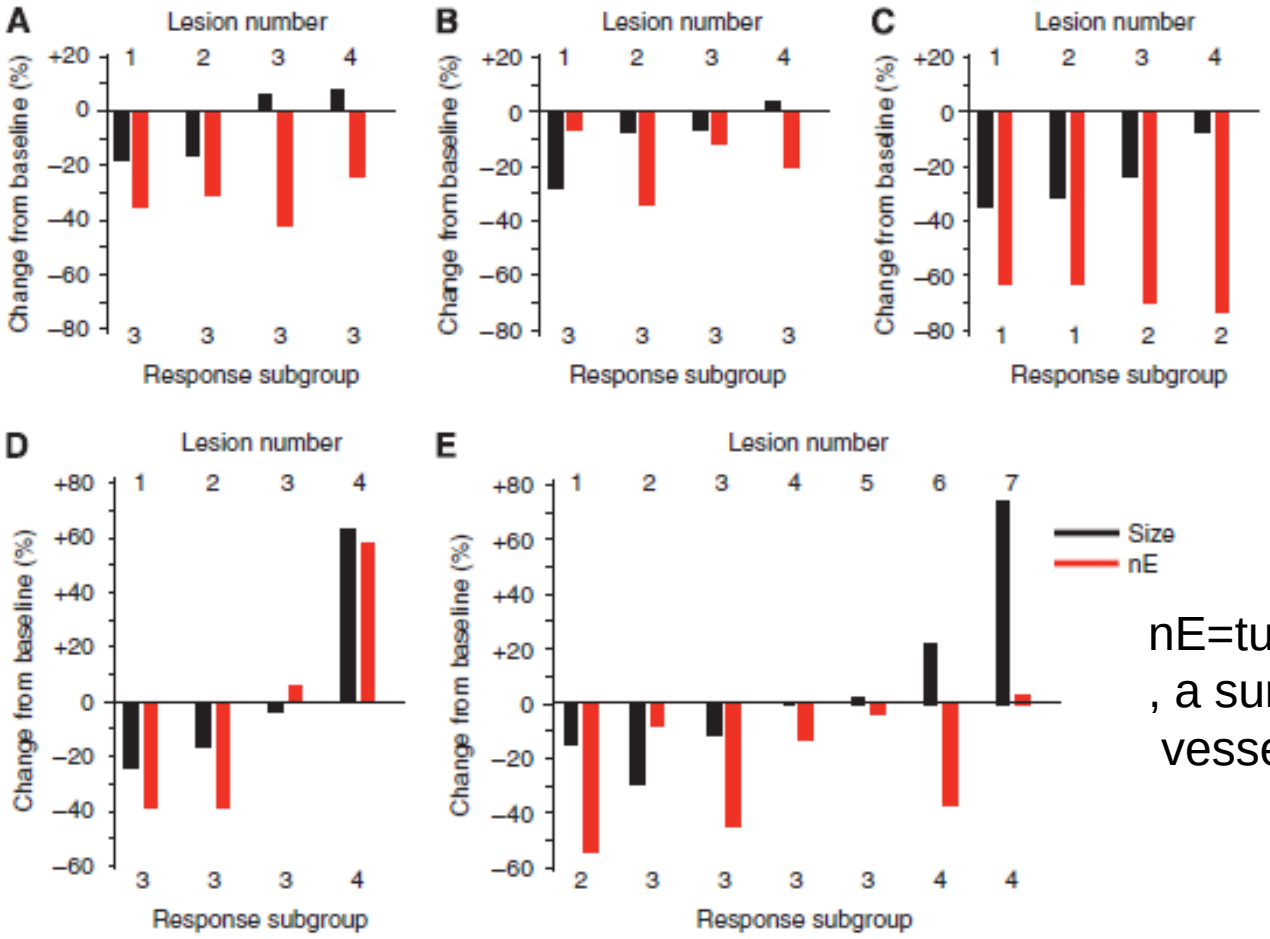




Heterogeneity in individual biomarkers at a protein level



Individual metastasis within patients behaving differently.



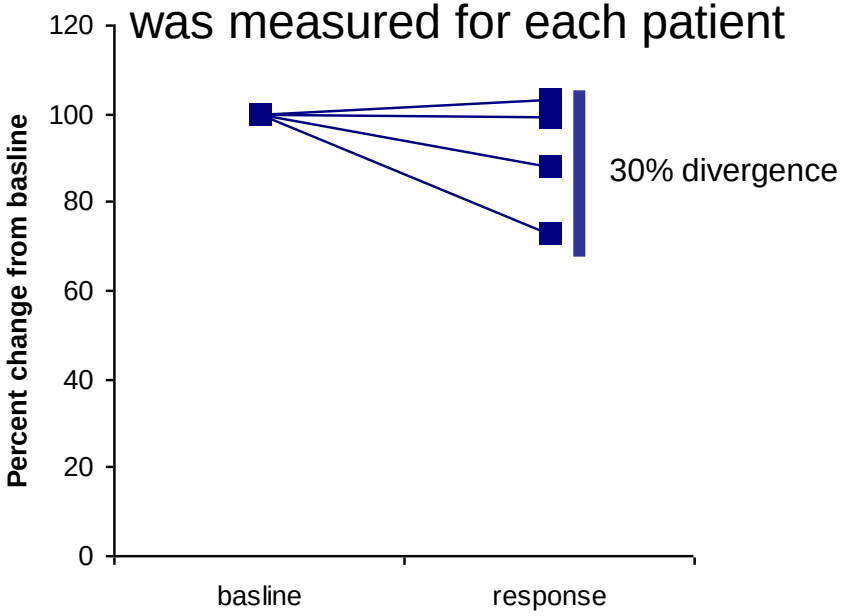
nE=tumor enhancement , a surrogate marker of vessel density

Vasudev BJC 2013

The relationship between heterogeneity within tumors and divergent responses

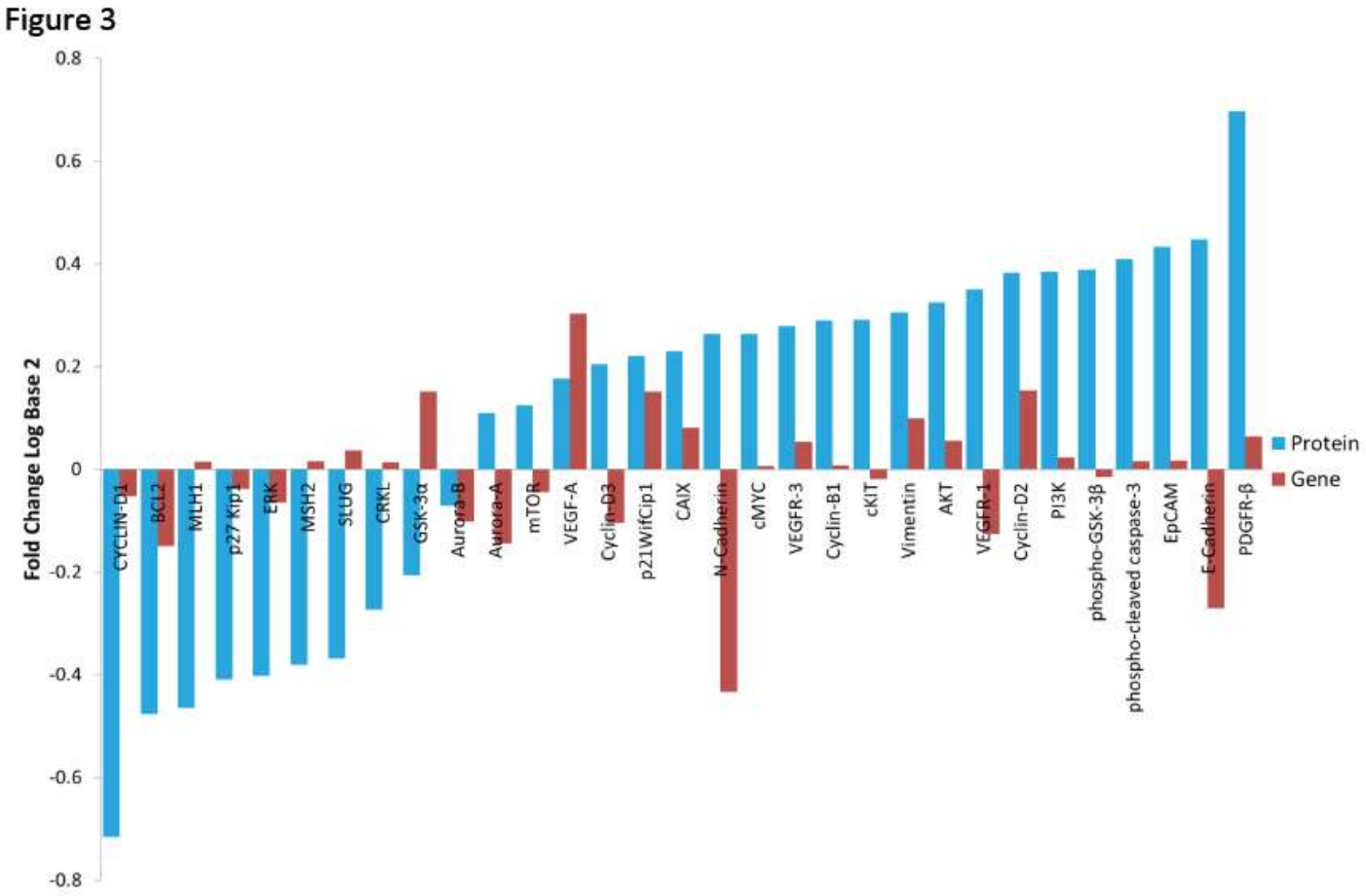
Hierarchical clustering results

A response divergence score was measured for each patient

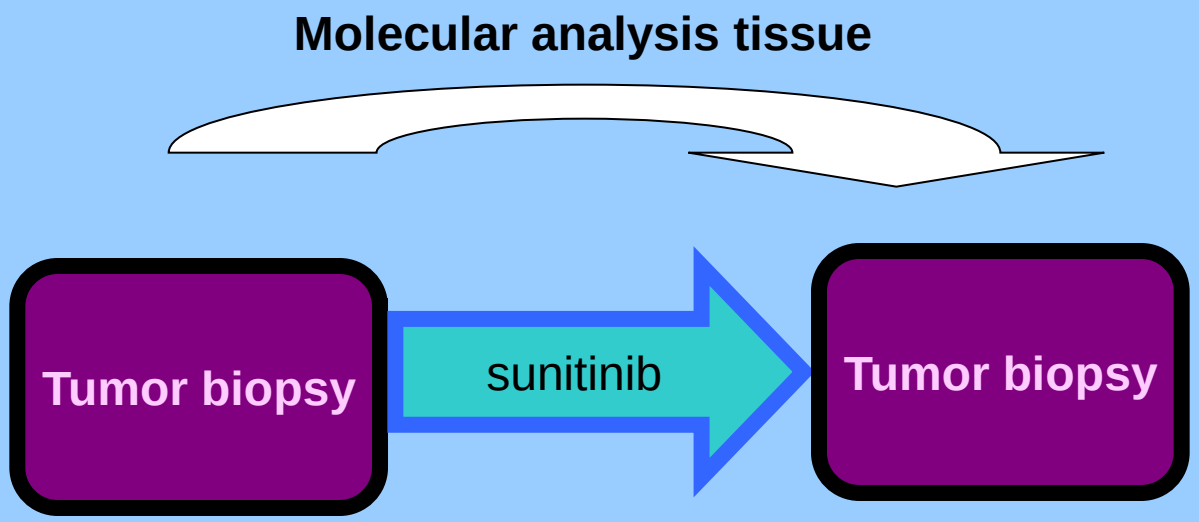


- Multiple samples from each RCC tumor
- GCH array performed to identify clustering
- Divergent radiological response measured
- Correlation between clustering and radiological diversity plotted.

Lack of consistency of VEGF targeted therapy on gene and protein expression.

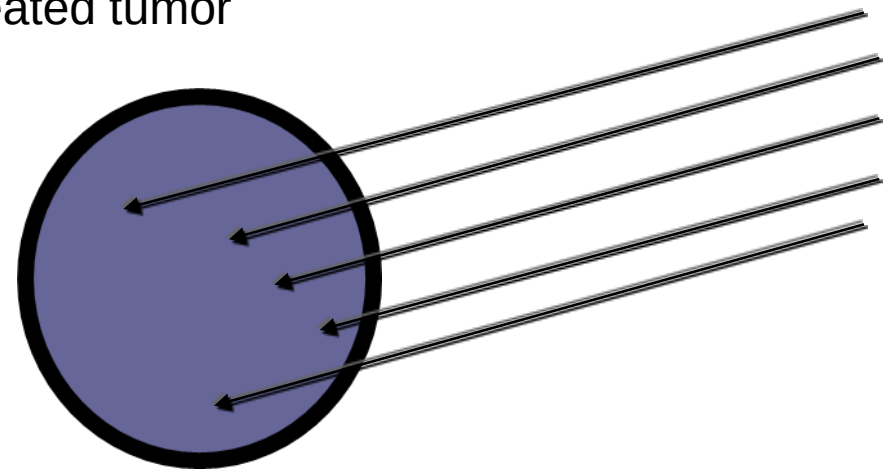


Changes in biomarker expression with targeted therapy exploring resistance.



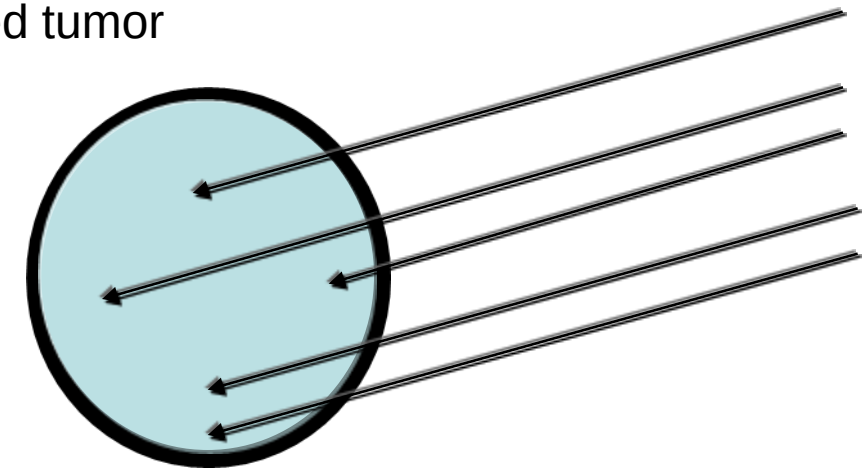
Can any consistent changes be identified from this tissue?

Untreated tumor



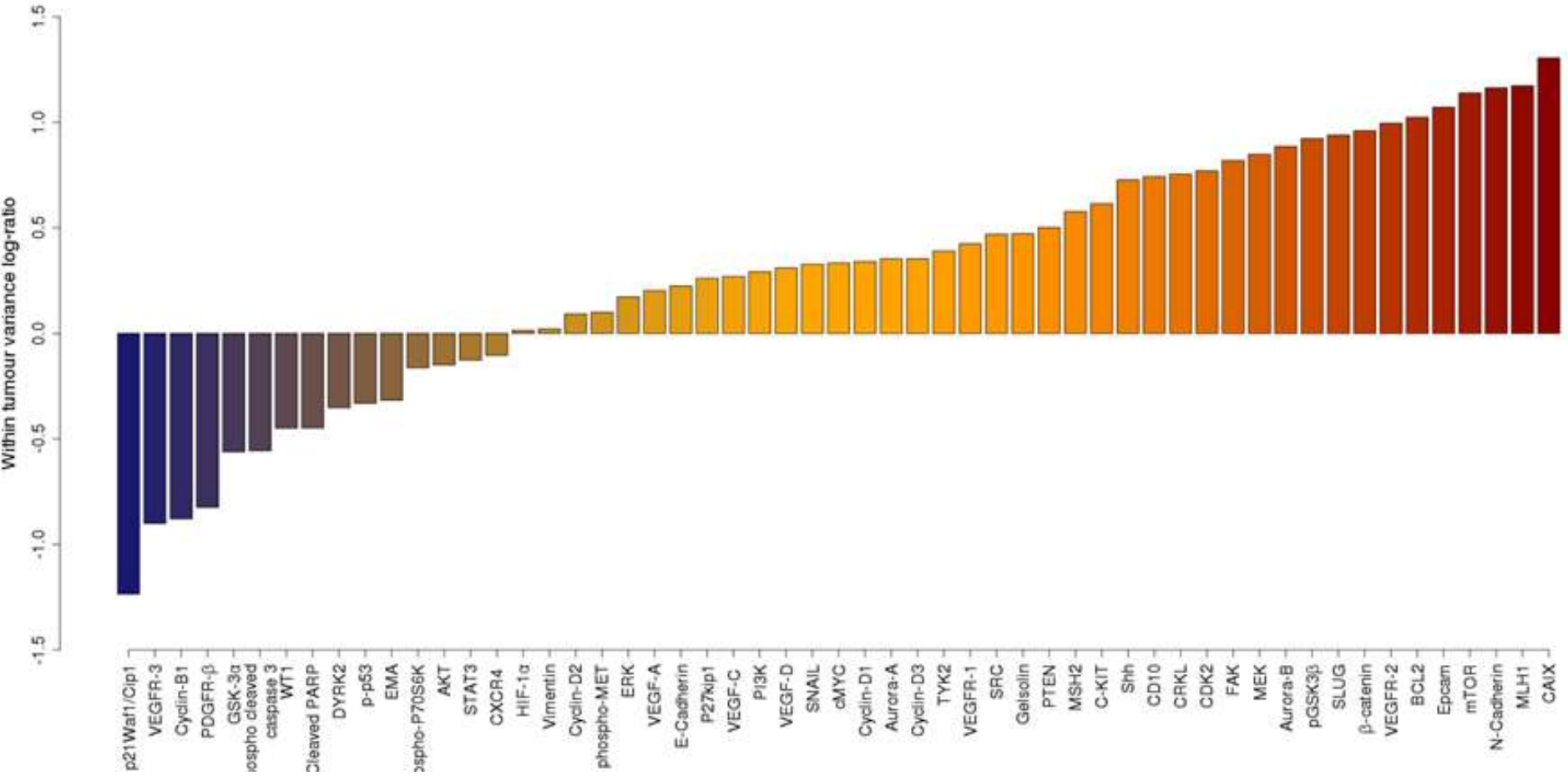
Multiple frozen biopsies from untreated tissue

Treated tumor



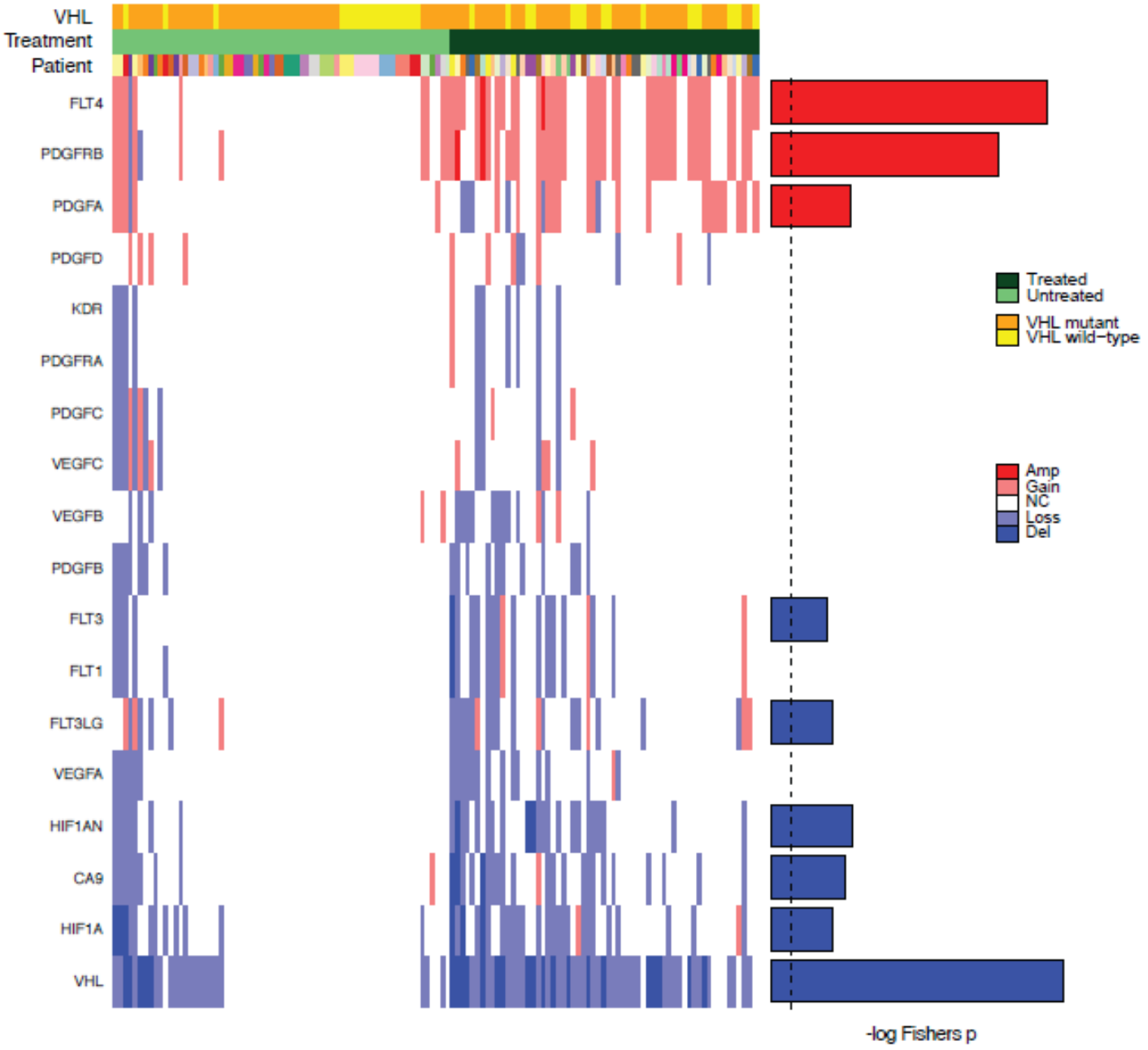
Multiple frozen biopsies from treated tissue

Protein variability increases with VEGF targeted therapy

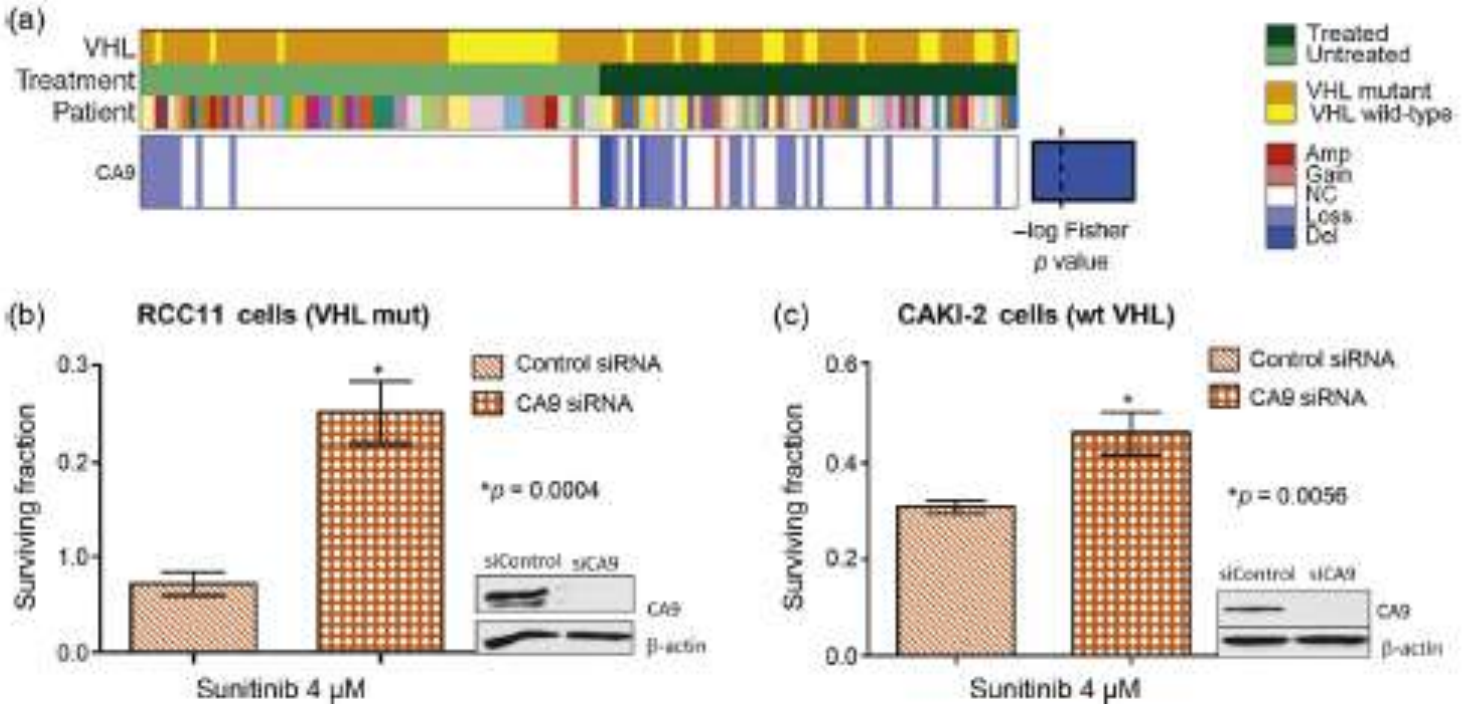


Stewart et al GU ASCO 2013

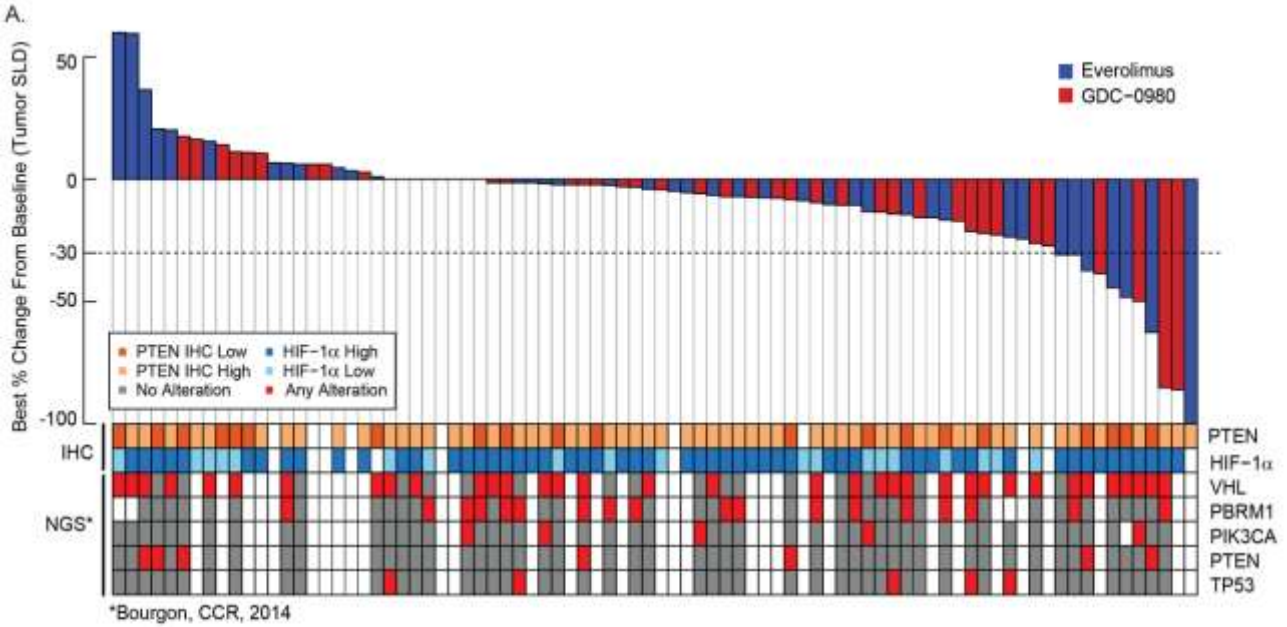
Dynamic genetic changes with sunitinib (CGH array before and after therapy)

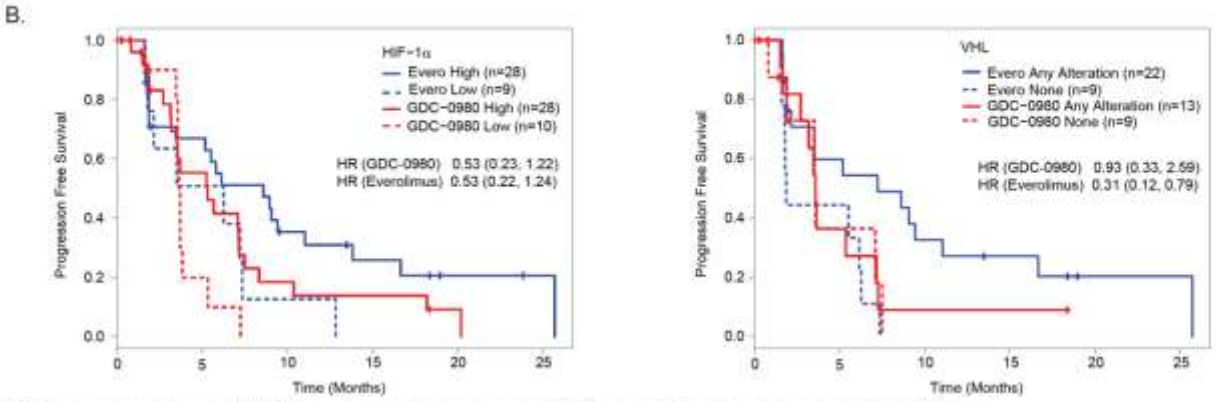


Chromosomal changes to CA9 gene with VEGF targeted therapy.



Biomarkers for mTOR inhibitors in VEGF resistant disease.

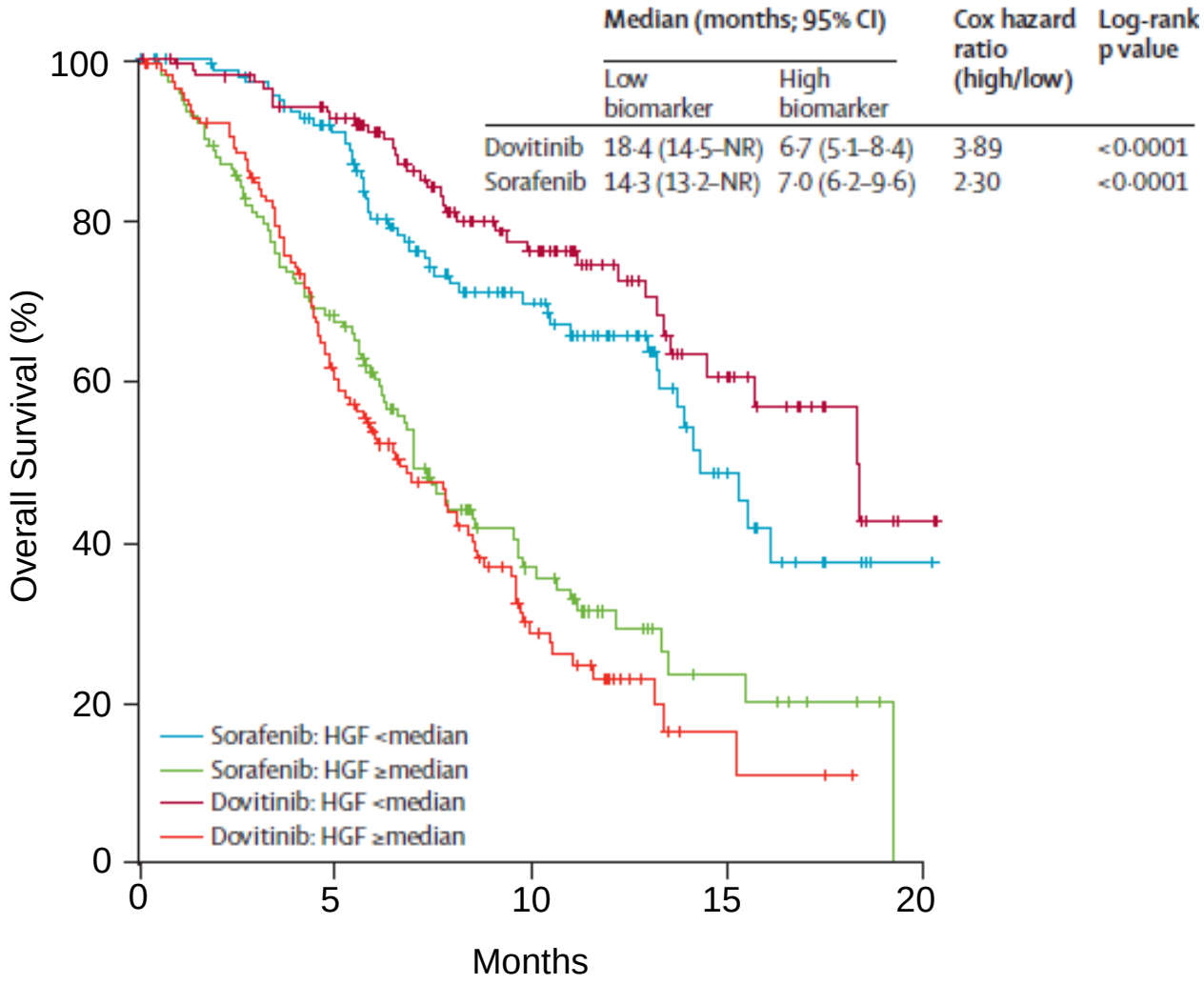




IHC = immunohistochemistry; NGS = next generation sequencing; SLD = sum of the longest diameters of target lesions

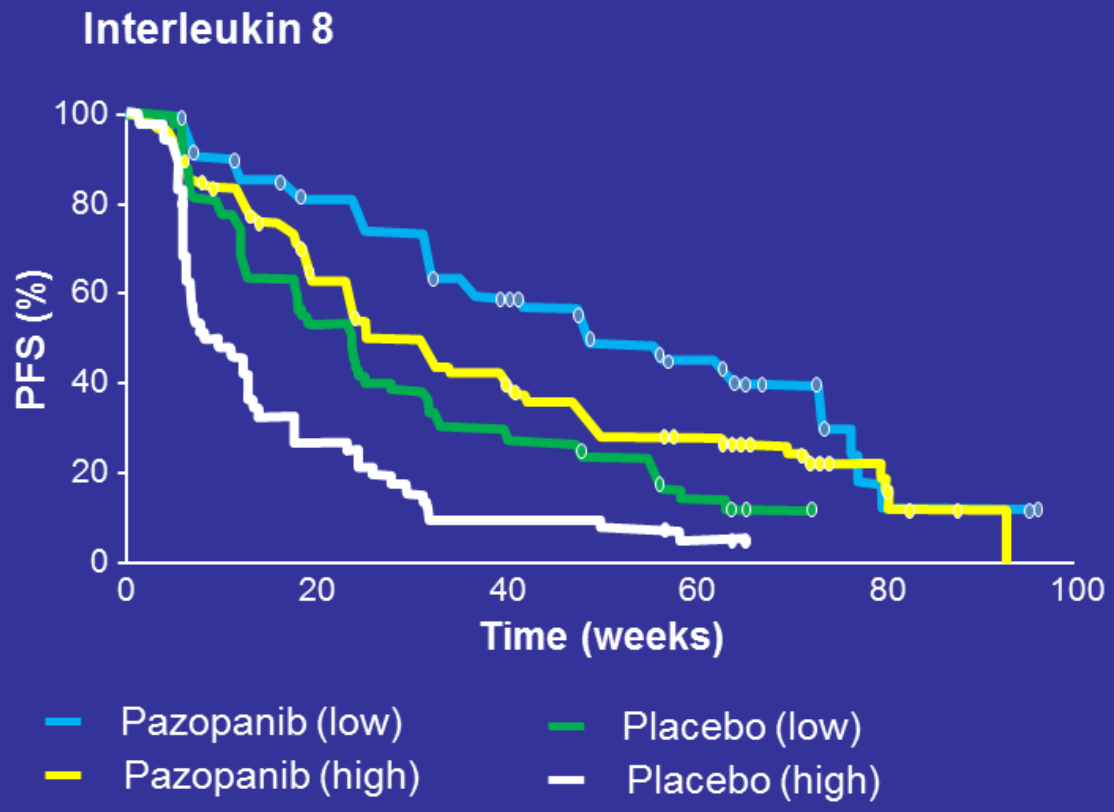
Biomarker development

HGF as biomarker in RCC



Motzer et al., Lancet Oncology; 2014:15; 286-296

High levels of il-8 associated with a good poor prognosis.



1. Tran HT, *et al. Lancet Oncol* 2012;13:827-837.

Genome Wide Association Study

- GWAS: test millions of genetic variants across the entire genome for their association with diseases, traits, or clinical outcomes
  - NHGRI GWAS Catalog: a curated resource of single nucleotide polymorphism (SNP)-trait associations

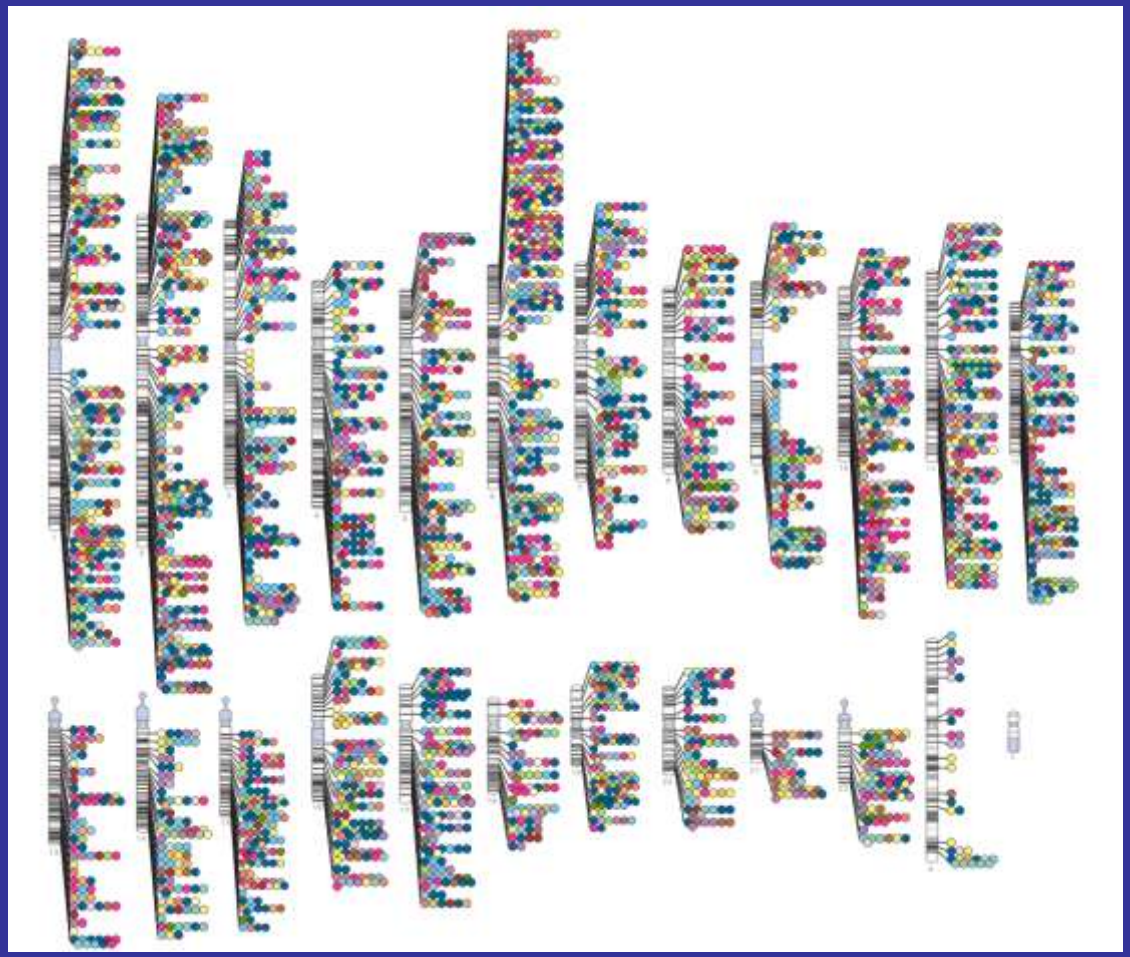


Image courtesy of the National Human Genome Research Institute, July 2013; http://www.genome.gov/GWAStudies/

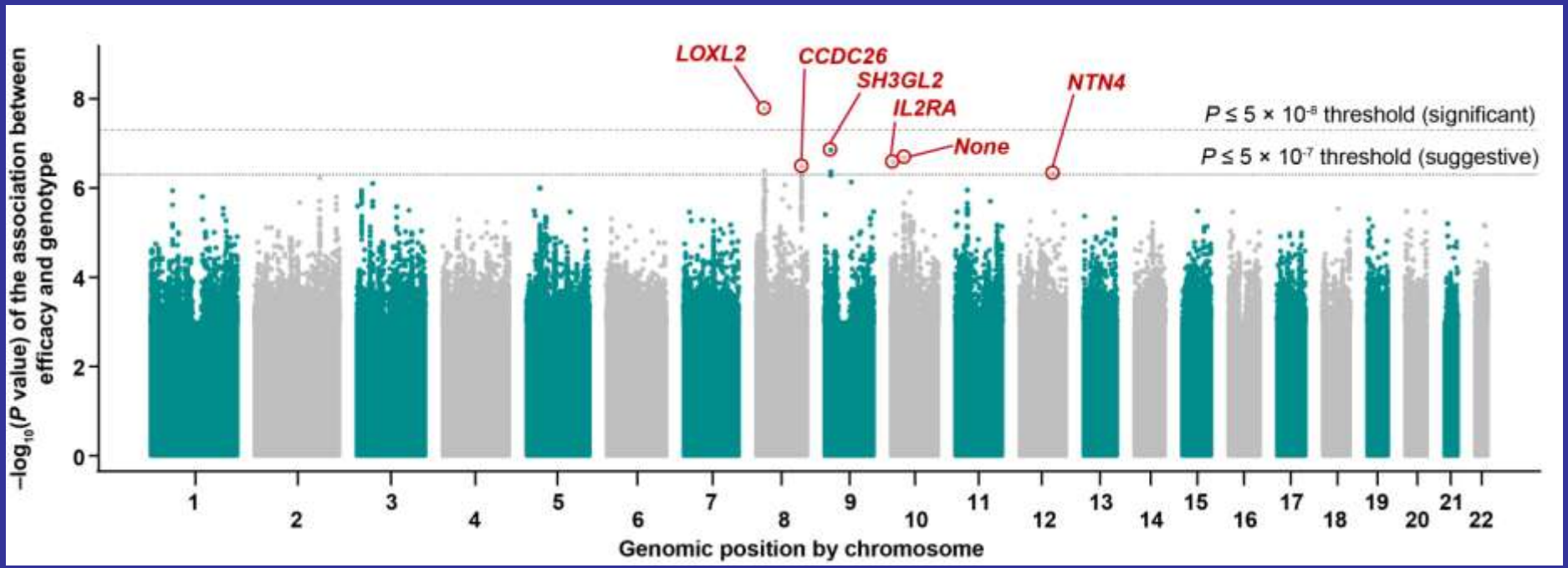
GWAS in Renal Cell Carcinoma (RCC)

- GWAS have identified genetic variations associated with the risk of developing RCC[1]
- GWAS have not been used to identify genetic predictors for response to treatment in metastatic RCC
  - Prior reports were candidate gene studies
- This GWAS evaluated germline SNPs as potential biomarkers for efficacy and adverse events following treatment with the tyrosine kinase inhibitors (TKIs) pazopanib and sunitinib

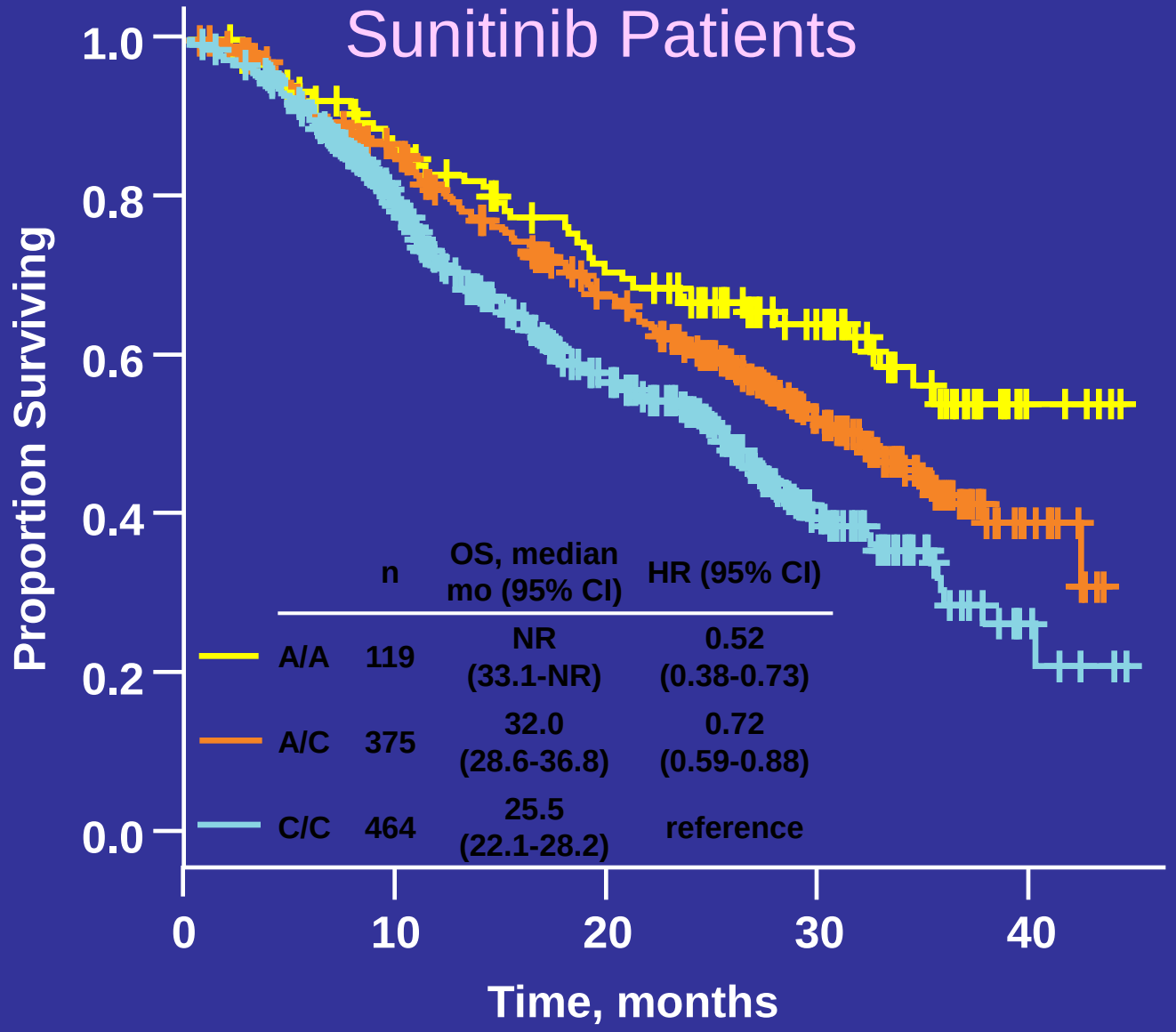
1. Purdue et al. *Nat Genet.* 2011;43:60.

GWAS Efficacy Results

- At genome-wide significance level ($P \leq 5\times10^{-8}$)
  - No variants were associated with efficacy in separate pazopanib and sunitinib PGx populations
  - A *LOXL2* variant was associated with the multi-endpoint test in the combined PGx population
- Suggestive associations at $P \leq 5\times10^{-7}$
- 5/6 variants are in genes possibly relevant to RCC



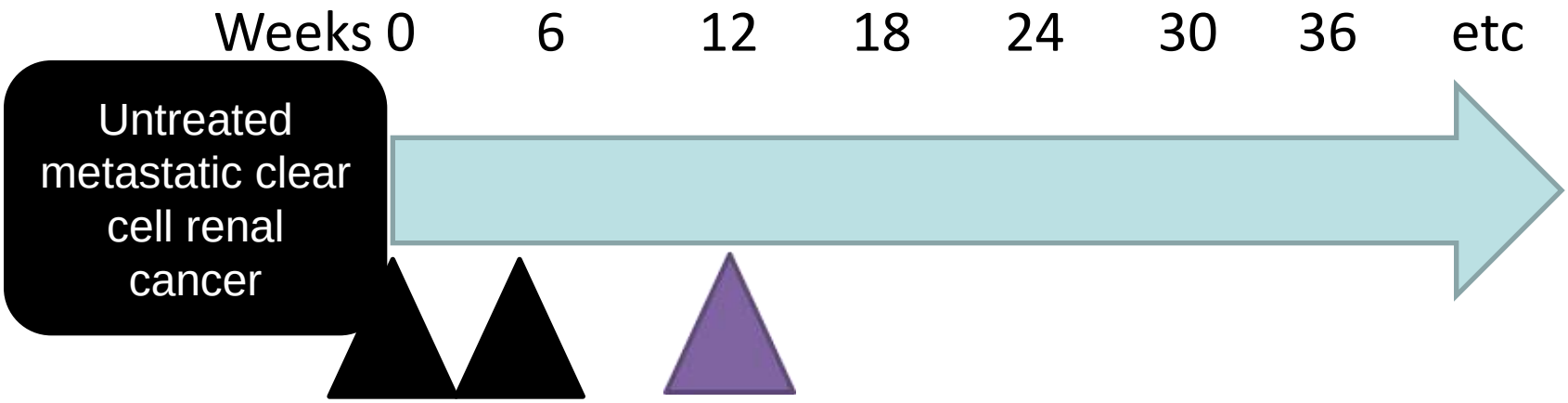
Variant Genotype (A/A) in *LOXL2* Intron Associated with Longer OS in Pazopanib and Sunitinib Patients



CI, confidence interval; HR, hazard ratio; mo, month(s); NR, not reached; OS, overall survival.

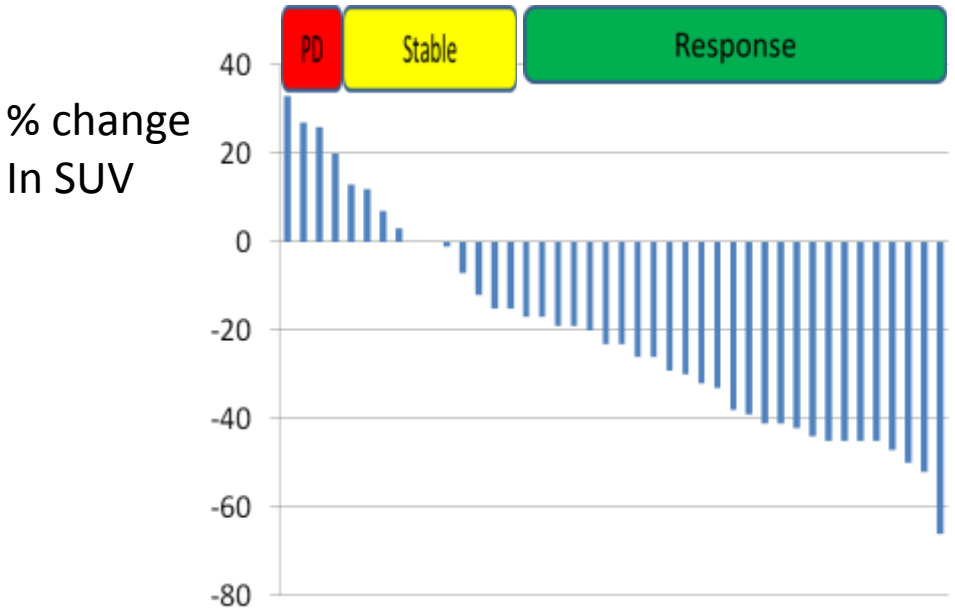
Biomarker development

Sequential FGD-PET in mRCC patients treated with sunitinib.



FDG-PET CT scans were performed 2 days after the completion of cycle 1 and 3

A high proportion of patients have a PET response* after 6 weeks of sunitinib- but it does not predict outcome.

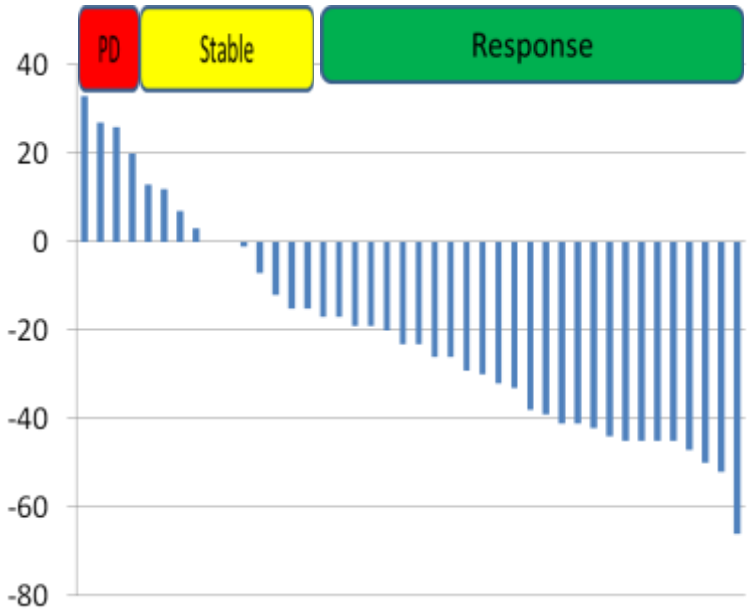


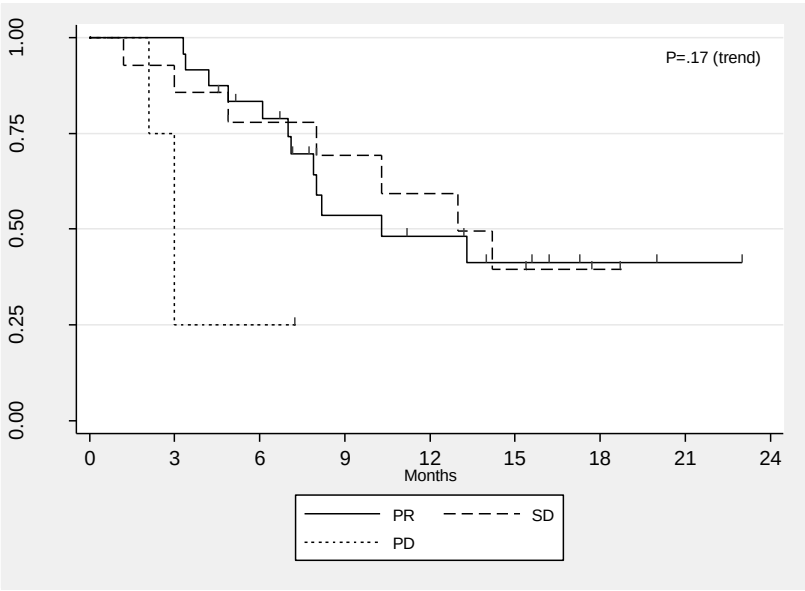
* Respnose = 20% reduction in SUVmax

Kayani et al CCR 2011

A high proportion of patients have a PET response* after 6 weeks of sunitinib- but it does not predict outcome.

% change
In SUV





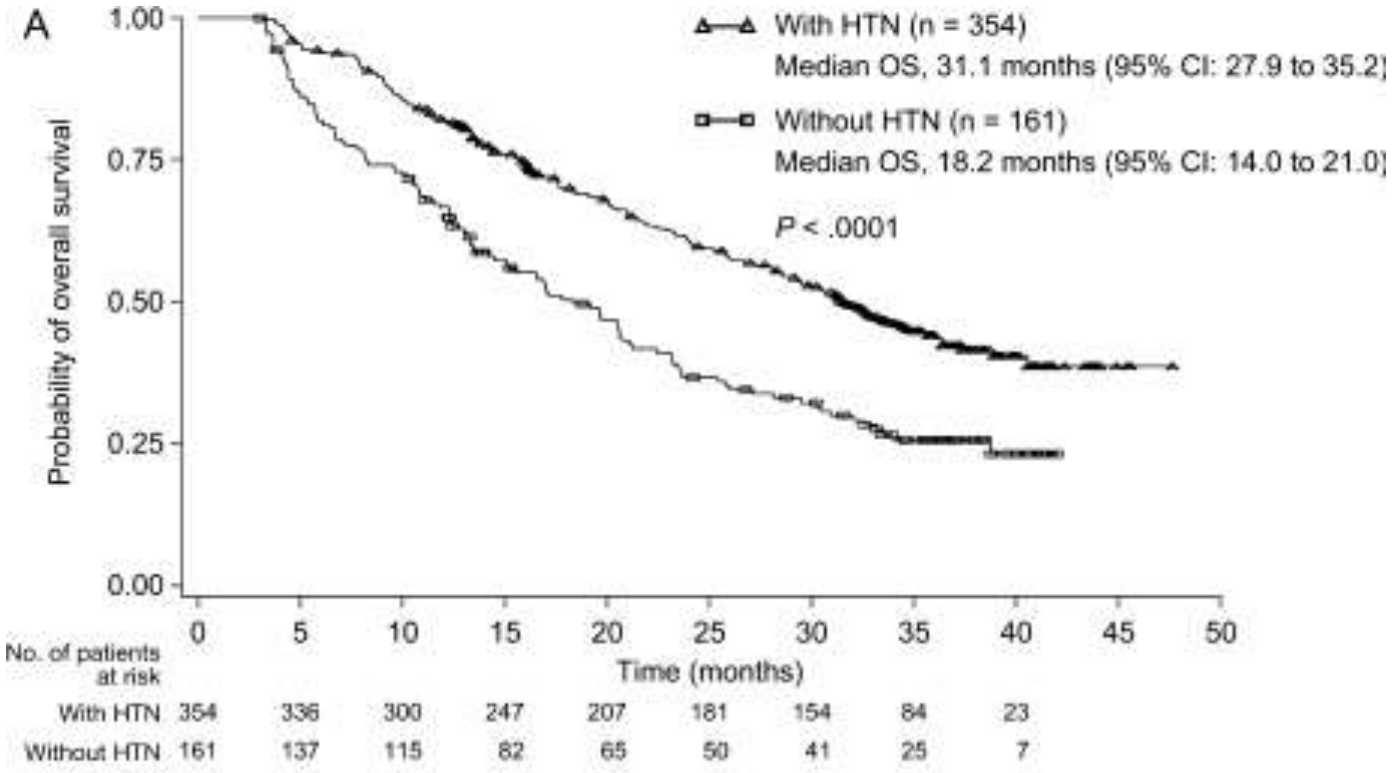
* Respnose = 20% reduction in SUVmax

Kayani et al CCR 2011

Hypertension in RCC patients treated with axitinib.

- VEGF targeted therapy causes vasoconstriction.
- This is likely to be ‘on target’ and measurable sequentially.
- Does it correlate with outcome?

Hypertension as a biomarker in RCC.



	With HTN			Without HTN		
Month	N	S	95% CI	N	S	95% CI
10	300	85.5%	(81.4 to 88.8)	115	72.4%	(64.7 to 78.6)
20	207	66.9%	(61.5 to 71.6)	65	46.7%	(38.6 to 54.5)
30	154	52.8%	(47.2 to 58.1)	41	31.4%	(24.0 to 39.1)

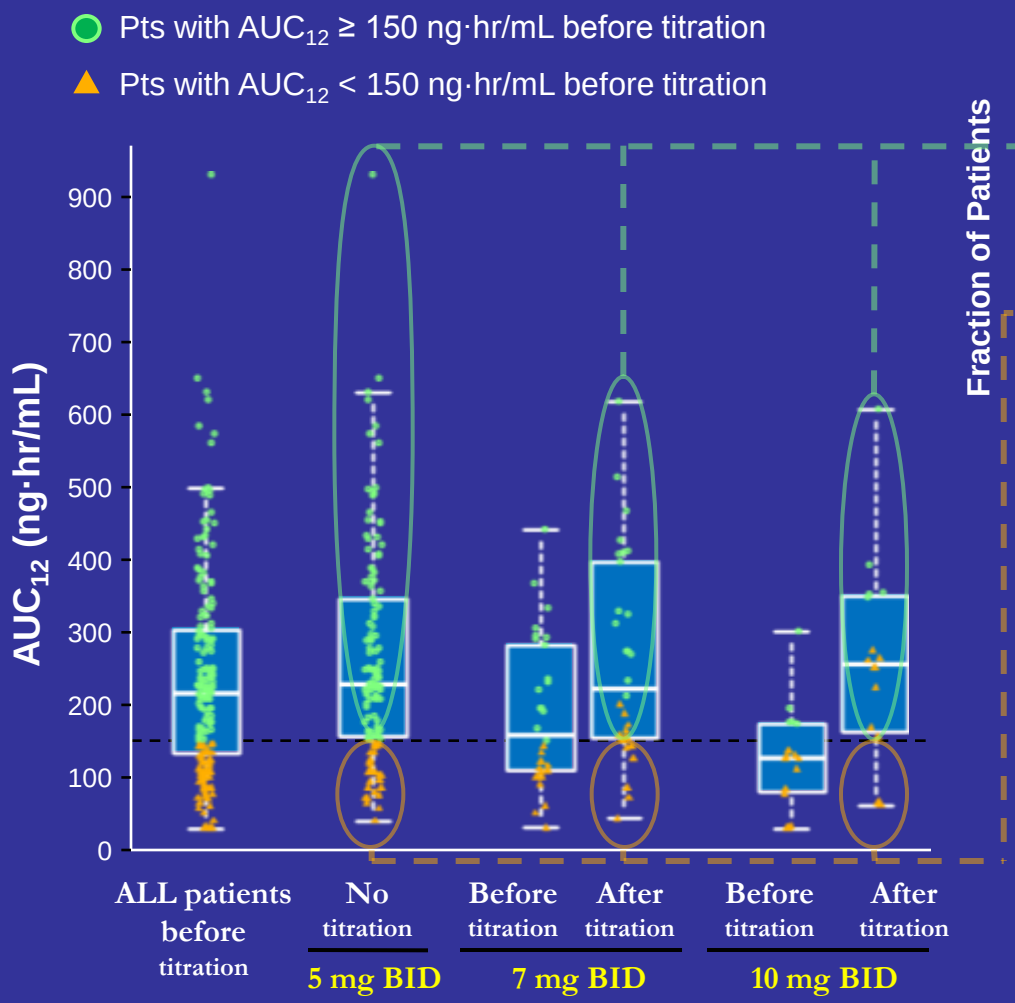
Rini et al., JNCI: 2011 May 4;103(9):763-73

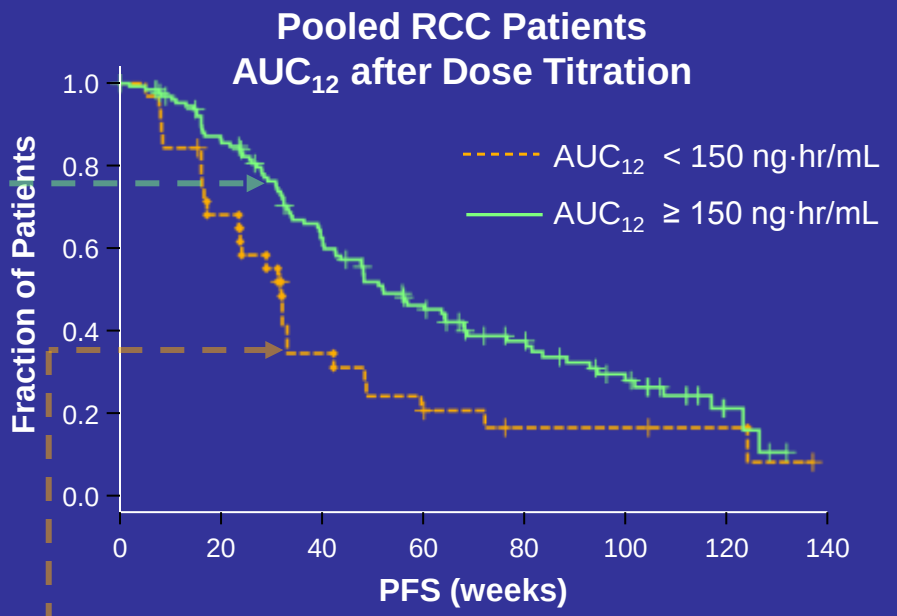
Therefore if we dose titrate to hypertension can we improve outcomes.

- Prospective trial in untreated patients.
- All patients get axitinib.
- Randomisation to dose escalation to hypertension.
- Blood levels correlated with outcome (AUC).

Response rates were higher in dose escalation group- but not outcome was not longer.

Axitinib 1st line PFS vs Exposure: Retrospective Analysis of Phase II RCC Data



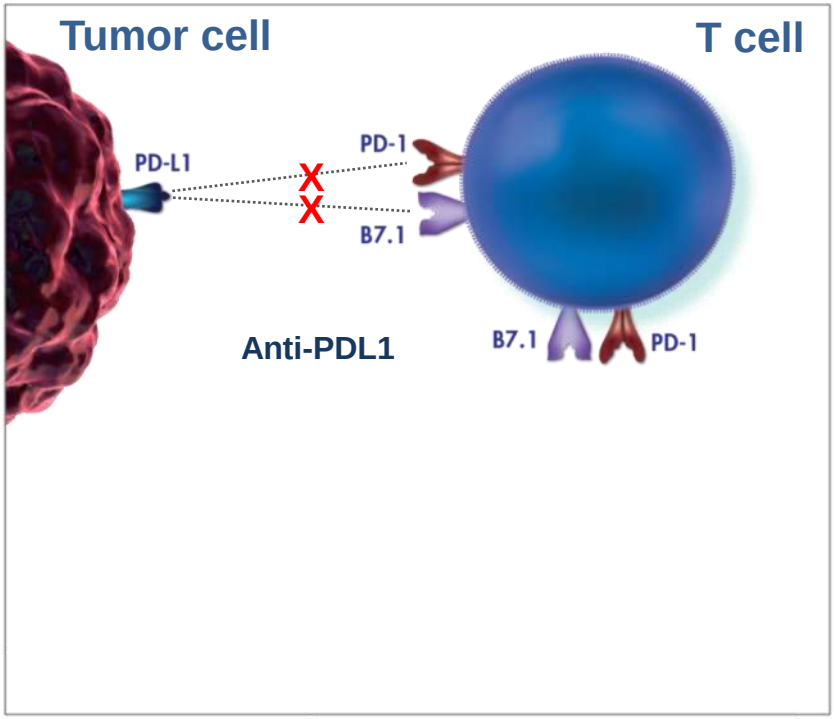


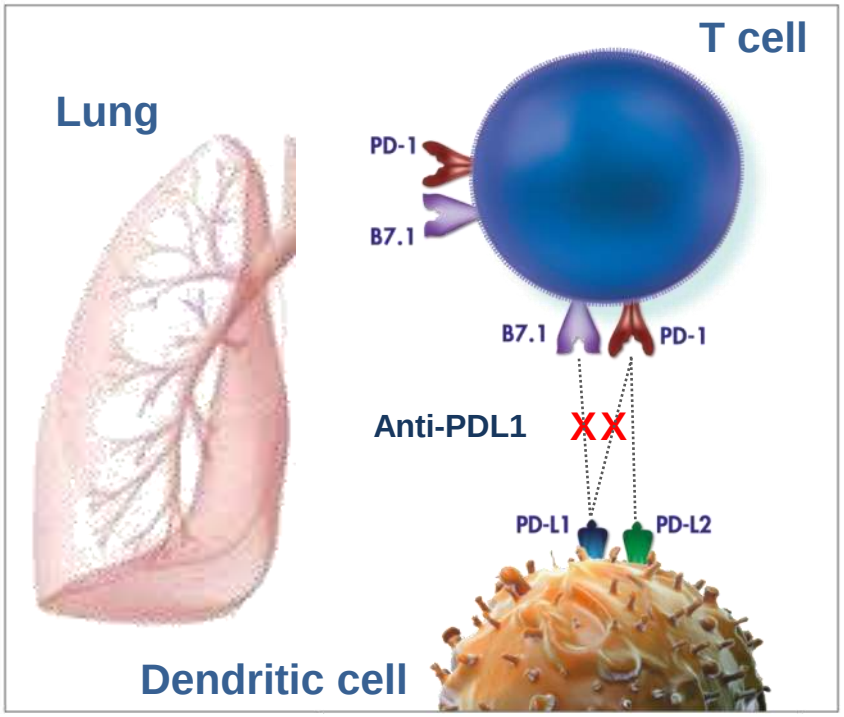
AUC_{12} = area under the plasma concentration-time curve from 0 to 12 hr

Rini et al., ASCO 2012

Biomarker development

MPDL3280A Is an Engineered Anti-PD-L1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1



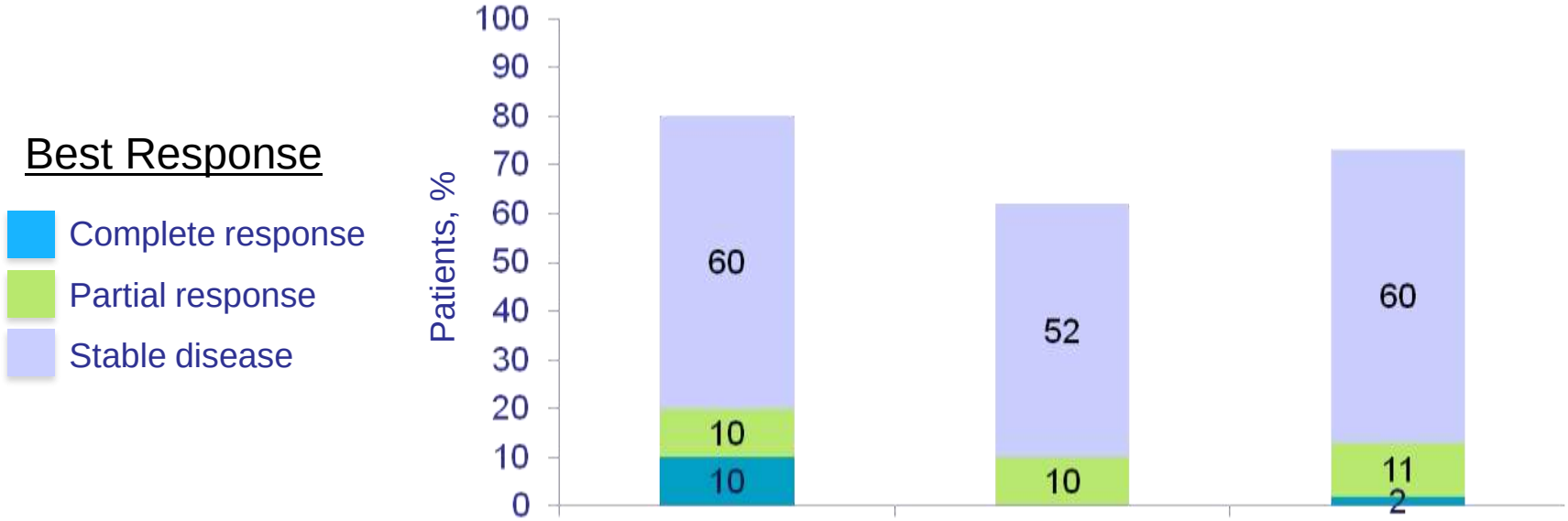


- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming
- MPDL3280A leaves the PD-L2/PD-1 interaction intact, maintaining immune homeostasis and potentially preventing autoimmunity

Presented by: Prof. Thomas Powles

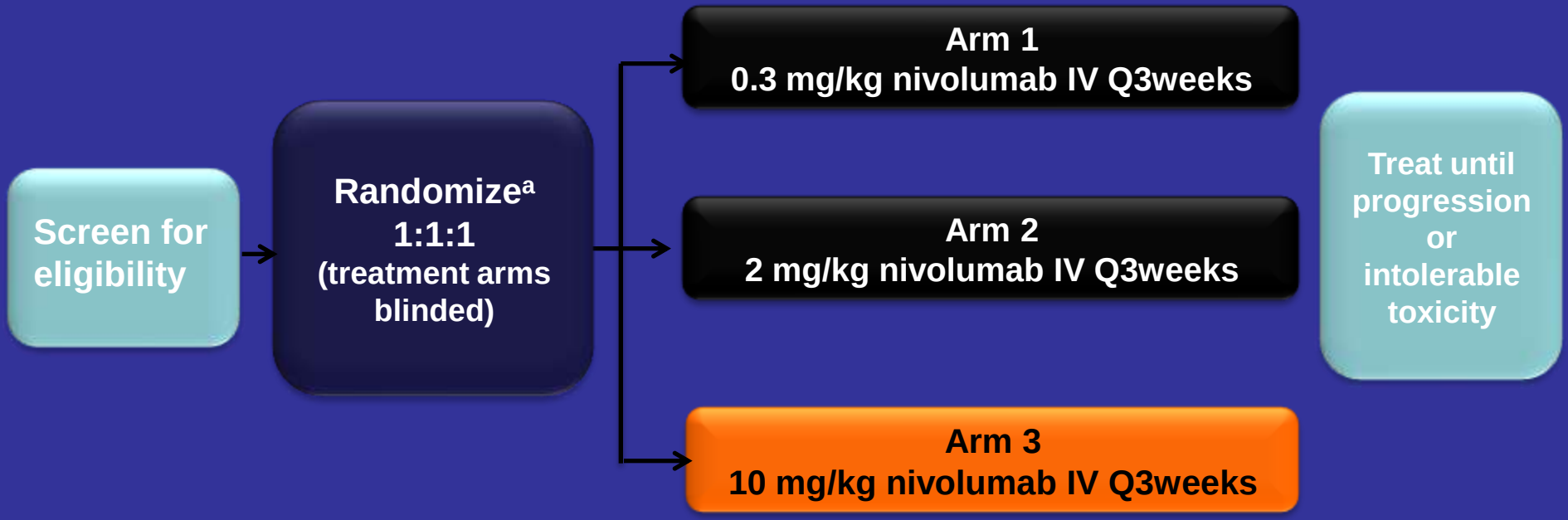
MPDL3280A: Summary of Response by PD-L1 IHC Status

Investigator-Assessed Best Overall Response Rate (ORR*), % (n/N)			
	PD-L1 Positive	PD-L1 Negative	All†
Overall population (N = 140)	36% (13/36)	13% (9/67)	21% (29/140)
RCC (N = 47)	**20% (2/10)**	**10% (2/21)**	**13% (6/47)**



* ORR includes investigator assessed unconfirmed and confirmed PR/CR by RECIST 1.1.
† 16 patients with RCC were of unknown status.
Patients dosed at 3-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.

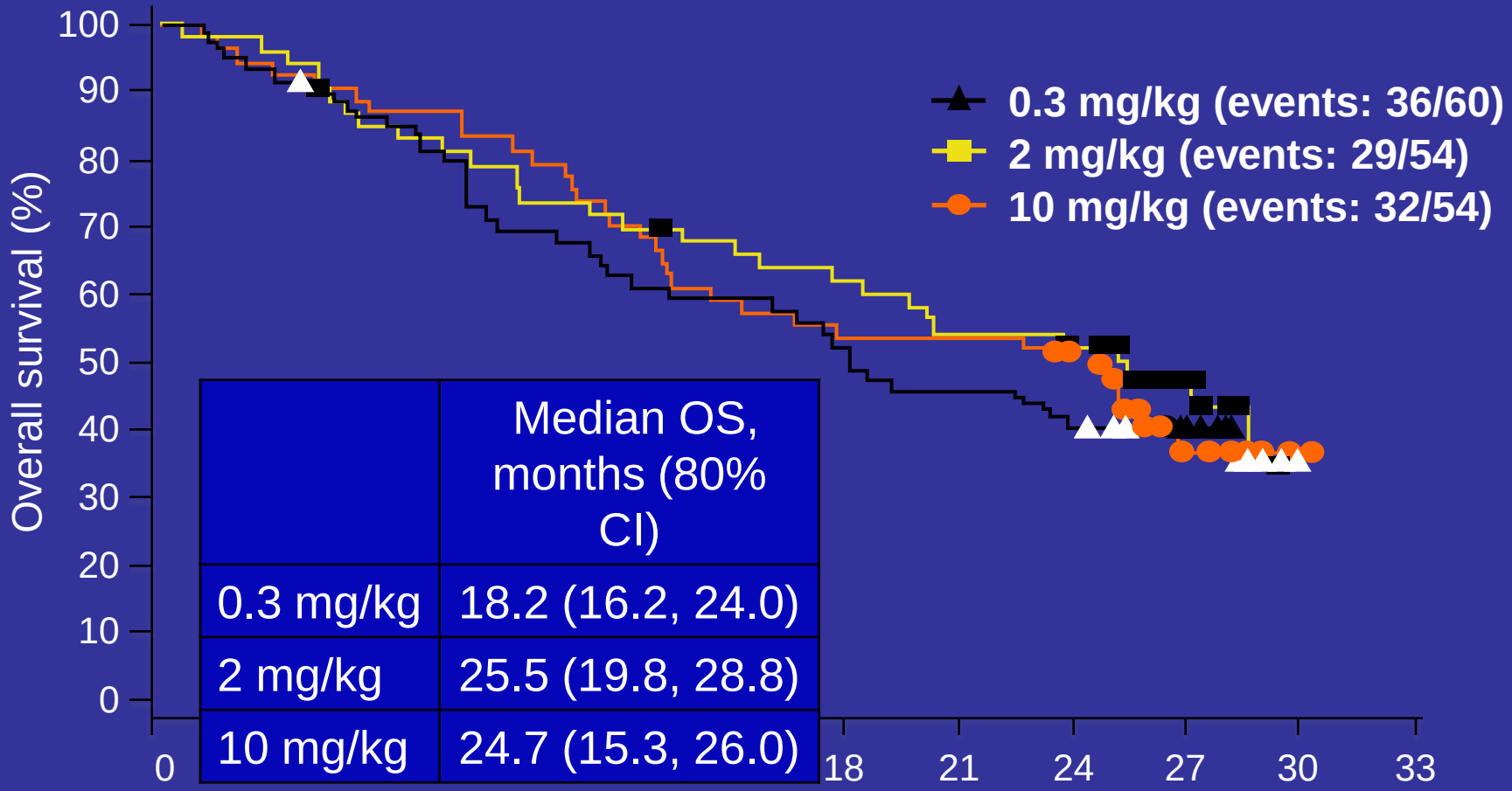
Phase II study design



ClinTrials.gov NCT01354431

[a]Stratified by MSKCC prognostic score (0 vs 1 vs 2/3) and number of prior lines of therapy in the metastatic setting (1 vs >1).

Overall survival



	Median OS, months (80% CI)
0.3 mg/kg	18.2 (16.2, 24.0)
2 mg/kg	25.5 (19.8, 28.8)
10 mg/kg	24.7 (15.3, 26.0)

Number of patients at risk

0.3	60	56	50	41	37	35	31	27	24	13	0	0
2	54	52	45	42	38	35	32	28	26	12	0	0

Based on data cutoff of March 5, 2014; Symbols represent censored observations.

Conclusions

- We have good prognostic markers but no validated predictive biomarkers.
- Hypertension may be our best predictive marker-but we don’t do anything about it.
- Real time biopsies may be required, but it may be better to look at free circulating tumor DNA.
- Treated tissue is at least as complex as untreated tissue (maybe more complex).